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# Extra gene makes mice manic

**But common drug can be used to control symptoms.**

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A gene whose abnormalities have been associated with symptoms of schizophrenia, epilepsy and autism also has comparable effects when artificially duplicated in mice.

Duplication of a single gene — and too much of the corresponding protein in brain cells — causes mice to have seizures and display manic-like behaviour, a study has found. But a widely used drug reversed the symptoms, suggesting that it could also help some people with hyperactivity who do not respond to common treatments.

Smooth functioning at the synapses, the junctions between brain cells, is crucial to functions that control everything from social etiquette to everyday decision-making. It is increasingly thought that some neuropsychiatric disorders are caused by function of the synapses going awry[1], and indeed researchers have found that neuropsychiatric conditions such as schizophrenia and autism can sometimes be traced to missing or mutated copies of *SHANK3*[2], a gene that encodes one of the 'architectural' proteins that help to ensure that messages are relayed properly between cells. Some people with attention deficit hyperactivity disorder (ADHD), Asperger's syndrome or schizophrenia have an extra copy of a wider region of DNA that contains *SHANK3*[3].

To explore the role of *SHANK3*, Huda Zoghbi, a neurogeneticist at Baylor College of Medicine in Houston, Texas, and her colleagues created mice with duplicate copies of the gene. “The mouse was remarkably hyperactive, running around like mad,” says Zoghbi. But the animals did not respond to stimulant medications typically used to treat ADHD. Instead, their hyperactivity grew much worse. “That’s when we knew this was not typical ADHD,” says Zoghbi. The study is published today in *Nature*[4].

The paper is a “really good example of the importance of gene dosage”, says Thomas Insel, director of the US National Institute of Mental Health in Bethesda, Maryland. “It matters a lot whether you have no copies, one copy, two copies” or more of a given gene, he says.

**Human parallels**

In addition to hyperactivity, the mice displayed a combination of mania-like behaviours and seizures, which are indicative of a disorder called hyperkinesia. When the researchers sifted through clinical databases, they found records of two people whose psychiatric profiles resembled those of the mice, and who also carried a duplication of *SHANK3*. One had bipolar disorder and epilepsy; the other

had seizures and ADHD characterized by hyperactivity, poor attention and compulsive behaviour. Like the mice, this person had not responded well to amphetamines used to treat ADHD.

After trying various treatments, the researchers gave the mice valproate, an anticonvulsant and mood-stabilizing drug commonly used to treat bipolar disorder and epilepsy. Remarkably, the drug reversed the psychiatric effects. The results suggest that excess *SHANK3* protein drives a psychiatric syndrome that can be treated effectively.

Joe Gleeson, a paediatric neurologist and geneticist at the University of California, San Diego, says that the study is “one of the first to explore, in a comprehensive way” the importance of gene dosage in mouse neurological disorders. He says that the paper addresses the underpinnings of these disorders on all fronts, from psychopharmacology to proteomics and human genomics, and notes that “the results are all in alignment”.

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## References

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